

REVIEW ARTICLE

Opioid-induced bowel dysfunction: prevalence, pathophysiology and burdenS. J. Panchal,¹ P. Müller-Schwefe², J. I. Wurzelmann³**OnlineOpen:** This article is available free online at www.blackwell-synergy.com**SUMMARY**

As a result of the undesired action of opioids on the gastrointestinal (GI) tract, patients receiving opioid medication for chronic pain often experience opioid-induced bowel dysfunction (OBD), the most common and debilitating symptom of which is constipation. Based on clinical experience and a comprehensive MEDLINE literature review, this paper provides the primary care physician with an overview of the prevalence, pathophysiology and burden of OBD. Patients with OBD suffer from a wide range of symptoms including constipation, decreased gastric emptying, abdominal cramping, spasm, bloating, delayed GI transit and the formation of hard dry stools. OBD can have a serious negative impact on quality of life (QoL) and the daily activities that patients feel able to perform. To relieve constipation associated with OBD, patients often use laxatives chronically (associated with risks) or alter/abandon their opioid medication, potentially sacrificing analgesia. Physicians should have greater appreciation of the prevalence, symptoms and burden of OBD. In light of the serious negative impact OBD can have on QoL, physicians should encourage dialogue with patients to facilitate optimal symptomatic management of the condition. There is a pressing need for new therapies that act upon the underlying mechanisms of OBD.

Introduction

Given the negative fundamental effect pain can have on quality of life (QoL), the philosophy underpinning the World Health Organization's (WHO's) three-step analgesic ladder is to free patients from pain (1). This compassionate position supports an aggressive approach to pain management, with progressively stronger analgesics recommended until relief is achieved.

As many cancer patients suffer from moderate-to-severe pain, opioids are the mainstay of analgesic therapy for treating this population (2). Opioid analgesics are also used for the treatment of chronic non-cancer-related pain, including musculoskeletal and neuropathic pain (3). While there is a paucity of good-quality research concerning the risks and benefits of the long-term use of opioids for chronic non-cancer pain, their efficacy *per se* is acknowledged in these patients (4).

Surveys of treatments for pain, either related to cancer or non-related, have revealed wide variations in the use of opioids across countries (5,6). Irrespective

Review Criteria

Comprehensive literature review of MEDLINE.

Message for the Clinic

There should be greater appreciation of the prevalence and burden/impact of opioid-induced bowel dysfunction and the need to effectively manage symptoms of the condition.

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Disclosures

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of these variations, a large number of patients are currently receiving opioid therapy for chronic pain. Globally, it has been estimated that a total of 365 million prescriptions were written for opioids in 2005 [235 million prescriptions in the USA (7), 66 million in the EU and 64 million in the rest of the world (8)]. A substantial proportion of these prescriptions were for chronic pain: in the USA 20% of prescriptions were for opioid therapy of over 30 days' duration (7).

A large-scale computer-assisted telephone survey was recently undertaken to explore the prevalence, severity, treatment and impact of chronic pain (6). The survey, conducted in 15 European countries and Israel, found that chronic pain of moderate-to-severe intensity occurred in 19% of adults, seriously affecting the quality of their social and working lives. Approximately 60% of those reporting moderate-to-severe pain had experienced the problem for 2–15 years, and 70% were under the care of their family doctors/general practitioners for pain management. More than half (52%) of chronic pain sufferers were taking some form of prescription

analgesic, the most common class of which was non-steroidal anti-inflammatory drugs (44% patients); strong opioids were used by 5% of the 46,394 patients surveyed (6).

The aim of palliative care is to improve the QoL of patients (and their families) who face life-threatening illness. In addition to providing spiritual and psychosocial support, patients should be offered effective symptom and pain relief (1). Therefore, the use of opioid analgesics is unsurprisingly very common in the palliative care setting. For example, in the US, opioid pain medications are used in the terminal phase of care for more than 50% of cancer patients (9).

While opioids are the gold standard for treating pain when analgesics such as acetaminophen and aspirin do not achieve adequate control (1), adverse effects compromise their therapeutic potential. The gastrointestinal (GI) tract is a significant site of opioid-related adverse effects due to the presence of opioid receptors, whose activation by exogenous opioids, in particular, disrupts GI motility and secretion, thereby inhibiting normal bowel function (10). This action commonly causes bothersome GI side effects, the most common of which is constipation; others include decreased gastric emptying (leading to gastro-oesophageal reflux/heartburn), abdominal cramping, spasm, bloating, delayed GI transit and the formation of hard dry stools. In turn, this can cause straining, painful defecation, incomplete evacuation and a sensation of anorectal bowel obstruction (10–13). The action of opioids on the GI tract is also thought to contribute to nausea and vomiting (14). However, in contrast to nausea and vomiting, patients rarely develop tolerance to the constipation-related adverse effects of opioid use (13,15). In addition to GI effects, prolonged opioid therapy can lead to cellular and intracellular changes, which may contribute to pharmacologic opioid tolerance and/or increased sensitivity to pain (manifested as apparent opioid tolerance), resulting in the need for dose escalation. Prolonged opioid treatment may also result in hormonal changes, such as reduced testosterone and oestrogen levels, and may even alter immune function (16).

The constellation of GI signs and symptoms associated with opioids is referred to as opioid-induced bowel dysfunction (OBD) (13,17). OBD, the most common and often most debilitating symptom of which is constipation, can have a significant adverse impact on patients taking opioids (13,15). This paper will provide an overview of the pathogenesis and burden of OBD and will summarise current management strategies.

Pathophysiology

To understand the basis of OBD, the physiology of the GI tract and the role of the endogenous opioid system in the alimentary canal must be considered. The GI tract is innervated by the enteric nervous system, which is composed of the myenteric plexus, located between circular and longitudinal smooth muscle layers of the bowel, and the submucosal plexus, located in the submucosa (10,18). Enteric neurons also synthesise opioid peptides and their transmitters.

Met-enkephalin, leu-enkephalin, β -endorphin and dynorphin are examples of endogenous opioids present in the GI tract, where they have been localised to both neurons and endocrine cells of the mucosa (10). Studies in animals and humans suggest that endogenous opioids inhibit enteric nerve activity and inhibit both propulsive motor and secretory activities (10,11). Therefore, endogenous opioids in the GI tract appear to function to co-ordinate the contractile process under normal conditions and suppress intestinal motility when required (such as during inflammation, stress and trauma) (10,19).

Immunocytochemistry and mRNA quantification techniques have identified receptors that mediate the effects of both endogenous and exogenous opioids on bowel function (10,18). Three major and distinct classes of opioid receptors are located in the enteric nervous system: delta, kappa and mu (20,21). Of these three receptor classes, the enteric mu-opioid receptor appears to be the principal mediator of opioid agonist effects on the GI tract (20,22). When opioid agonists bind to these receptors, the release of excitatory and inhibitory neurotransmitters is inhibited. This interrupts the co-ordinated rhythmic contractions required for intestinal motility and reduces mucosal secretions (23,24). Administration of exogenous opioids can cause OBD by decreasing peristalsis (11), which in combination with reduced secretions into the gut and increased reabsorption of fluid from the gut (as the stool remains in the intestinal lumen for extended periods) leads to the formation of dry, hard stools that are difficult to pass.

Burden of OBD

The burden of OBD is a function of its prevalence as well as its negative impact on health-related QoL. While the existence of OBD is undisputed, its wider impact is likely underestimated by healthcare professionals (25), particularly because most OBD symptoms persist for as long as opioid therapy is administered. The physical sequelae of constipation, some of which can very occasionally be life threatening, also demand consideration when assessing the

burden of OBD. Haemorrhoids, diverticular disease and fecal impaction contribute to the burden of the condition and often require treatment (26).

Constipation is the most common and often most debilitating adverse effect associated with opioid therapy for the management of chronic pain (13,15). Perhaps because of this, estimates of the prevalence of OBD are largely based on the frequency of this primary symptom (13). To assess the true prevalence of OBD, there is clearly a need for large-scale, prospective studies that use a standardised definition of the condition that embraces all symptoms of OBD.

Estimates of the frequency of constipation vary from 15–90% in patients receiving opioids for non-cancer pain (12,3,27). A meta-analysis of available randomised, placebo-controlled trials of non-cancer patients receiving opioids for moderate-to-severe pain revealed that approximately 80% of patients experienced at least one adverse event, with constipation (41%) and nausea (32%) being the most common opioid-related side effects (3). However, according to a systematic review of 34 randomised, controlled trials of oral opioids, 15% of patients reported constipation (12). The difference between these two analyses can be attributed to the exclusion of trials of 'weak' opioids, such as codeine and tramadol, in the former study and the inclusion of comparator trials in the latter. A higher rate of constipation (90%) was reported in a multicentre, international, open-label, crossover trial comparing the efficacy and tolerability of transdermal fentanyl and sustained release oral morphine in 256 patients aged 26–82 years with chronic non-cancer pain (27).

It is particularly challenging to obtain accurate estimates of the prevalence of constipation caused by opioid therapy in cancer patients because of numerous other factors that may also induce the condition. These include physiologic causes such as dehydration, metabolic disturbances such as hyperkalaemia, mechanical causes such as tumour and psychological factors. However, it is clear that cancer patients experience constipation relating to opioid use, and that existing disease-related constipation can be exacerbated by opioid therapy (13,28).

The prevalence of OBD symptoms, including constipation, was assessed in 593 cancer patients receiving treatment according to WHO guidelines (29). Constipation was one of the most frequent side effects of opioid treatment, observed in 23% of patients. Another series of studies conducted in a large US hospice found that 40–63% of patients with cancer had opioid-induced constipation (25). The higher rate (63%) was derived from retrospective patient reports; the lower rate corresponded to data obtained from a chart audit (40%).

Much of this wide variation in the frequency of opioid-induced constipation can be attributed to study design and population heterogeneity. Study populations vary with respect to age, gender and underlying pathology. Choice of opioid, route of administration, dose and the duration of treatment all contribute to variation in the frequency of side effects. Subjectivity introduces additional variation: people's perceptions of constipation vary, as does their approach to the management of symptoms. A fundamental reason why reported rates of constipation vary so greatly is that no single definition of constipation is universally applied. While many study protocols, for reasons of convenience and consistency, define constipation as fewer than three bowel movements per week, attempts have been made to refine the definition by taking a more comprehensive approach. For example, the Rome diagnostic criteria for constipation not only encompass bowel movement frequency, but also capture the discomfort associated with constipation (Table 1) (30). This more comprehensive definition should ideally form the basis of any tool used to assess constipation associated with OBD.

Impact of OBD

Evidence shows that the long-term use of opioids for chronic pain can lead to improvements in patients' QoL (28,31). However, the side effects of opioid therapy, e.g. constipation, are likely to limit this benefit (9). Illustrating this point, one survey has indicated that constipation is ranked by the majority of cancer patients as an even more common source of distress than the pain they are suffering (32). It has also been suggested that some patients receiving long-term opioid treatment for pain would rather endure their pain than the constipation opioids may cause (9).

Attempts have been made to quantify the impact of OBD on health-related QoL (33,34). The Patient Reports of Opioid-related Bothersome Effects survey – a web-based cross-sectional survey of 161 chronic pain patients in the USA taking oral opioids and generally using laxatives – was conducted to characterise the prevalence, frequency and severity of OBD symptoms, and their impact on QoL and activities of daily living (ADL). Participants were asked to identify any GI side effects they had experienced during opioid treatment, and rate the impact of each symptom on QoL and ADL on a five-point scale. The most common side effect was constipation, with 85–95% and 74–92% of these constipated patients reporting some degree of negative impact on QoL and ADL, respectively (35). OBD symptoms other

Table 1 Rome II and III criteria for chronic constipation (30)

Diagnostic criteria	Symptoms
Rome II In at least 12 weeks, which need not be consecutive, in the preceding 12 months, ≥ 2 symptoms must be present	<ul style="list-style-type: none"> • Straining in $> 25\%$ of bowel movements • Hard or lumpy stools in $> 25\%$ of bowel movements • Sensation of incomplete evacuation in $> 25\%$ of bowel movements • Sensation of anorectal obstruction/blockade in $> 25\%$ of bowel movements • Manual manoeuvres to facilitate $> 25\%$ of bowel movements (digital disimpaction) • < 3 bowel movements per week • Loose stool is not present, and criteria for irritable bowel syndrome are not fulfilled
Rome III Presence of ≥ 2 symptoms	<ul style="list-style-type: none"> • Straining during $\geq 25\%$ of defecations • Lumpy or hard stools in $\geq 25\%$ of defecations • Sensation of incomplete evacuation for $\geq 25\%$ of defecations • Sensation of anorectal obstruction/blockage for $\geq 25\%$ of defecations • Manual manoeuvres to facilitate $\geq 25\%$ of defecations (digital manipulations, pelvic floor support) • < 3 evacuations per week • Loose stools are rarely present without the use of laxatives • Insufficient criteria for irritable bowel syndrome • Criteria fulfilled for the last 3 months, and symptom onset ≥ 6 months prior to diagnosis

than constipation, such as straining, incomplete evacuation and heartburn, have similarly been reported to have a significant detrimental impact on QoL and ADL (36).

Results of the 2004 National Health and Wellness Survey (a large, international survey that captured self-reported information on how patients use healthcare services) were used to assess the impact of opioid-induced constipation on healthcare resource utilisation, work productivity, and activity impairment in a sample of 2420 patients who had been taking opioids for ≥ 6 months for chronic pain (37). Compared with non-constipated patients, opioid-treated patients with constipation were more likely to visit physicians, miss work, feel that their performance at work was impaired and that symptoms impaired their ability to undertake daily activities (37).

Ultimately, OBD can impact the use of opioid medication. Patients may discontinue opioid therapy because of symptoms of OBD (3,17,38), which can pose challenges in achieving pain therapy goals.

Evaluation and treatment of OBD

Evaluation of OBD

Two constipation-specific instruments are available for patients to assess the impact and severity of the condition: the Patient Assessment of Constipation Quality of Life (PAC-QOL) and the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaires. The PAC-QOL instrument was developed to address the need for a standardised, patient-reported outcomes measure to evaluate the burden of constipation on patients' everyday functioning and

well-being over time, while the PAC-SYM instrument is used to assess the symptoms and severity of constipation. The PAC-QOL and PAC-SYM instruments have been shown to be reliable, valid and responsive measures of constipation and opioid-induced constipation respectively (39,40). Use of these brief and easy-to-administer questionnaires may help to characterise the extent and burden of OBD and thereby encourage a more active approach to treatment of the condition.

Treatment of OBD

After OBD has been recognised, steps should be taken to manage the condition; however, there are currently no detailed and widely accepted guidelines for the management of OBD. A well-recognised source of guidance is the European Association of Palliative Care Research Network (EAPC) who have published recommendations for treating adverse effects associated with opioids (41,42).

The EAPC recommends the following strategies for managing general adverse effects associated with oral morphine: reducing opioid dose, rotating opioids, changing the route of administration and symptomatic management (41). Unfortunately, each of these strategies appears to have limited benefit for most patients with OBD. The obvious disadvantage of reducing opioid dose is that analgesia may be compromised. Although there is much anecdotal and observational data to support switching opioids in the event of inadequate pain relief and/or intolerable side effects, there is a lack of randomised trials to vindicate this approach for reducing OBD (43). Similarly, although there is some evidence that transdermal administration of opiates such as fentanyl

Table 2 Common laxatives and side effects (13)

Laxative	Adverse effects	Mechanism of action
Stool softeners and emollients e.g. dioctyl sodium, docusate sodium	Few side effects, mainly bitter taste and nausea	Lubricates and softens stools
Stimulants and irritants e.g. senna and bisacodyl	Electrolyte imbalance, dermatitis, melanosis coli	Alters intestinal mucosal permeability; stimulates muscle activity and fluid secretions
Osmotic laxatives e.g. lactulose, magnesium salts, sorbitol	Electrolyte imbalance; excessive gas; hypermagnesaemia, hypocalcaemia and hyperphosphataemia in patients with renal dysfunction; dehydration	Osmotic effect of salts leads to greater fluid retention in bowel lumen and a net increase of fluid secretions in the small intestine
Bulk laxatives e.g. psyllium seed, bran	Increased gas; bloating; bowel obstruction if strictures present; choking if powder not taken with enough liquid	Increased fecal bulk and fluid retained in the bowel lumen
Non-absorbable solutions e.g. polyethylene glycol	Nausea; abdominal fullness; bloating	Volume lavage
Enema	Dehydration, hypocalcaemia and hyperphosphataemia in patients with renal dysfunction	Reflex evacuation

causes less constipation and is associated with better QoL than oral morphine (27), contradictory data also exist (44).

Symptomatic management

Addressing the individual symptoms of OBD (such as nausea, vomiting, gastric reflux and constipation-related symptoms) is currently the most viable option for relieving the condition. Understanding the mechanisms that cause OBD symptoms should inform treatment selection (45).

Nausea and vomiting associated with opioid use occur in approximately 25% of patients and tend to resolve over time. Patients who develop persistent, significant nausea/vomiting or are not satisfied with the approach of waiting for symptoms to resolve will likely benefit from an anti-emetic treatment with a prokinetic agent, such as metoclopramide, a dopamine antagonists or serotonin antagonist (45). To treat the gastro-oesophageal reflux associated with OBD, over-the-counter antacid and/or alginate preparations can provide effective symptom relief in many patients. Low-dose histamine H₂-receptor antagonists can also provide effective symptomatic relief, particularly in patients with milder symptoms. If these steps fail to provide adequate relief, proton pump inhibitors may be considered. These are agents of choice for the suppression of gastric acid production and have become the mainstay of therapy for acid-related diseases in general (46), although their utility in an OBD population has yet to be validated.

Current non-pharmacologic strategies for the constipation associated with OBD include interventions such as increased dietary fibre and fluid intake,

encouraging mobility and ambulation and encouraging daily bowel movements at the same time every day (13,45). However, pharmacologic approaches are often necessary. Laxatives are most frequently used to promote bowel movements in patients with opioid-induced constipation. Despite the wealth of laxatives available to treat constipation, an estimated 54% of patients treated for OBD do not achieve the 'desired result' with medication even half the time (13). Perhaps this limited efficacy should not be surprising in the context of the absence of treatments specifically designed for the treatment of OBD. Available laxatives do not target the underlying cause of OBD; furthermore, they are unpredictable, have a potential for over-use and dependency (both psychological and physical), and are associated with a range of side effects (see Table 2) (13,36,47).

In practice, stool softeners such as docusate sodium are commonly administered to patients with OBD; they are also prescribed prophylactically to patients on opioid regimens. Such agents are generally very well tolerated, but seldom achieve relief of opioid-induced constipation when used alone. Therefore, one of the most common regimens prescribed is a stool softener plus a stimulant laxative (e.g. senna) (13). Patients who do not respond well to this regimen are often offered a mild osmotic agent, lubricant or cathartic laxative. Bulk-forming laxatives should be recommended with caution because of the risk of exacerbating constipation, leading to intestinal obstruction unless adequate fluid intake is maintained. Therefore, bulk-forming agents are relatively contraindicated in cancer patients and older patients taking opioids for pain control.

Conclusion

Constipation is a recognised side effect of opioid use; however, its impact and the wider condition of OBD have been underestimated and underappreciated by healthcare professionals (25,38). In light of this, more studies specifically designed to assess the prevalence and burden of OBD are required.

Patients with OBD suffer from a broad range of symptoms which in turn can have a serious deleterious impact on QoL and the daily activities that patients feel able to perform (36). In an effort to relieve the most common and debilitating OBD symptom, constipation, patients often use laxatives chronically (which is associated with risks) or alter/abandon their opioid medication, potentially sacrificing analgesic efficacy (9,38). Therefore, the burden of OBD stems not only from the direct impact on QoL and healthcare resources of its many symptoms, but also from the side effects of treatments taken to relieve the condition. It is incumbent on the primary care physician to review patients' pain medication requirements regularly and to encourage dialog about side effects. Although symptomatic management can provide relief for some patients, there is clearly a need for new therapies that act upon the underlying mechanisms of OBD. Agents that specifically target the underlying cause of OBD are currently under investigation. The availability of these investigational agents may provide additional treatment options for physicians, and patients suffering needlessly from OBD.

Acknowledgements

Editorial assistance was provided by Amy Jackson, MPhil during the preparation of this manuscript; this assistance was supported financially by GlaxoSmith-Kline.

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Paper received March 2007, accepted April 2007